

Remarks

Claims 43-46, 49-53, and 55-57 remain pending. Claims 58 – 66 are hereby cancelled. Claims 43 and 55 are amended. No new matter is introduced with the present amendment.

Applicants thank Dr. Silverman for the interview of June 16, 2008, to discuss the pending claims.

The Office Action rejects claims 58 – 66 under §112, first paragraph as lacking written description. While Applicants disagree with the Examiner's arguments, Applicants cancel these claims in order to focus the application on the remaining claims. The subject matter of these claims remains available for claiming in a subsequent continuation application. This rejection, therefore, is no longer relevant to this application and Applicants request withdrawal.

The Office Action rejects claims 43 – 46, 49 – 53, and 55 under 35 USC §103(a) as obvious over *Norling et al.* (US 5,958,458) in view of *Buseti et al.* (US 5,788,987). Applicants request reconsideration. The cited references fail to establish a *prima facie* case of obviousness.

As discussed with the Examiner and as described in the application as filed, there are many synonyms in the art for the substrate of the present invention, including particle, bead, pellet, and the like. As discussed during the interview, Claim 43 is amended to impart a particulate size to the substrate of the present invention. Support for the amendment appears throughout the application as filed, with particular emphasis drawn to the figures and description of existing non-pareils in the art, where the substrate of the present invention is intended for use instead of such typical non-pareils. As noted by in the Interview Summary, the Examiner suggested an addition of particle size to the independent claim in order to distinguish the substrate of the present invention from coated tablets. Thus, the present claim amendment provides a contrast between the present invention, namely particles of less than 420 micron diameter, as opposed to conventional tablets, which typically range from 5,000 to 12,000 microns in diameter. As such, although both may be referred to as particulate, the substrate of the present invention is distinguishable from a tablet.

Thus, the present invention provides an effective pharmaceutical formulation that includes a single-ingredient substrate, where the majority of particles have a diameter of less than 420 microns. So, in addition to the recitation of size, the currently claimed invention requires a single-ingredient substrate. The cited references, however, describe a multi-ingredient substrate. Each reference describes a "core" that includes an active ingredient. In each reference, such cores are thereafter coated for purposes of modified release and the like.

The references do not teach or suggest a single-ingredient substrate. In fact, since the references propose multi-ingredient substrates, the references teach away from the single ingredient formulation of the present invention. Further, since the multi-ingredient substrates of the cited references achieve the stated purpose of the reference, there is no motivation to alter the formulations of the references. As such, the references fail to support a *prima facie* case of obviousness.

The primary reference, *Norling et al.*, describes a substrate that includes multiple ingredients. For example, at Col. 2, lines 8 – 32 of *Norling et al.*, the substrate, or “core” as that term is used in the reference, is described as having a w/w % composition of calcium phosphate along with additional components in order to impart a specified friability and flow angle. Further, *Norling et al.* describe the desired concentration of the active substance in the core at Col. 8, lines 18 et seq., followed by a description of the various coatings that may be employed. *Norling et al.* may not be used to support *prima facie* obviousness of a formulation with a single-ingredient core.

Similarly, the secondary reference, *Busetti et al.*, teach “a core including the pharmaceutically active agent(s).” *Busetti et al.* describe enteric coats that may be used over a multi-ingredient core in order to achieve a pharmacologically effective dosing regime to maintain blood plasma profiles overnight. While the Examiner points out the “one or more” phrasing in *Busetti et al.*, importantly, the one or more excipients is in addition to other ingredients. At Col. 4, lines 40 and 52, *Busetti et al.* describes that the excipients are in addition to the active ingredient. The active ingredient is the core, with additional ingredients added as described for preferred characteristics. *Busetti et al.* may not be used to support *prima facie* obviousness of a formulation with a single-ingredient core.

Applicants respectfully request that the Examiner withdraw the rejection and allow the pending claims.

The Examiner further rejects claims 56 and 57 as obviousness over *Norling et al.*, in view of *Busetti et al.*, and further in view of *Ekwuribe et al.*, relying on *Ekwuribe et al.* for a teaching of insulin drugs as active agents. Since *Ekwuribe et al.* fail to teach or suggest a single-ingredient substrate for pharmaceutical formulations as claimed in the present application, the *prima facie* case continues to fail for the reason outlined above. *Ekwuribe et al.* do not provide any further teaching or motivation to provide a pharmaceutical formulation of a single-ingredient substrate as claimed.

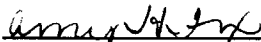
As described in the present specification, the single-ingredient substrate of the present invention has a variety of advantages over materials currently used in formulations. With regard to insulin products specifically, sugar spheres, even a modest amount in a pellet or core, may not be appropriate. Diabetic patients, both type I and type II, scrutinize their blood sugar levels. As such, even modest amounts may need consideration regarding a diabetic's caloric intake. A variety of publicly available references cite the dietary concerns of diabetic patients. As one example, reference is made to the *Handbook of Pharmaceutical Excipients*, page 510, copy attached hereto for ease of reference, where under "Safety" is noted "...sucrose is generally regarded as more cariogenic than other carbohydrates and in higher doses is also contraindicated in diabetic patients."

Further, although sugar spheres are typically not chemically incompatible with amine-containing active drug substances, such as insulin, sucrose may readily form glucose and fructose, which are known to be incompatible with amine groups, and, thus, potentially insulin. The formation of glucose and fructose from sucrose can be generated by acid-based hydrolysis or enzymatic action. Some small amounts of free glucose or fructose may be present in sucrose. In addition, some of the ingredients in spray coatings useful in formulations of the present invention may be acidic in nature and would tend to accelerate such a reaction. The glucose and fructose may react with the amine groups, in a Maillard reaction, resulting in discoloration and potentially degradation of the active ingredient. See, for example, US 6,264,989.

Applicants respectfully request withdrawal of the rejections and allowance of the pending claims. Should the Examiner have any remaining issues, he is encouraged to telephone the undersigned for expeditious handling.

Respectfully submitted,

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